REMARKS/ARGUMENTS

In response to the pending Office Action of January 11 , 2005, Applicant presents the following arguments and amendments. The present amendments are requested solely for the purpose of more clearly describing and claiming the present invention and do not introduce any new matter. Applicant submits that in light of the arguments and amendments presented this application is in condition for allowance. Accordingly, entry of these amendments, reconsideration of all pending rejections and objections, and passage to allowance is respectfully requested.

A Petition for a One Month Extension of Time and the required fees are provided with this response. With the entry of this amendment, claims 33-35, 61, 64, 68, 71, and 80 - 83 are pending herein.

Examiner Interview and Request for Information

Examiner Gregory W. Mitchell and Supervisor Examiner Sreeni Padmanabhan are thanked for their participation in telephone interviews on March 16th and March 17th, 2005. An Interview Summary describing the substance of this interview is submitted concurrently with the present response.

During the interview, Examiners Mitchell and Padmanabhan requested that Applicant clarify where in the specification support is provided for the limitation in claim 82 "wherein said particles are made by heating a carbon crucible having deposited thereon a detectable marker to a temperature in the range of 2250° C to 3000° C in an inert gas and in a sealed container, thereby generating particles suspended in said inert gas, and precipitating said particles suspended in said inert gas to form said diagnostic particles." Support for the this claim limitation is provided in the description of exemplary methods "for

forming a detectable reagent for use in labeling fibrin" beginning on line 25 of page 4 and ending on line 19 of page 5 which provides a description of the steps of (1) "heating a carbon crucible having deposited thereon a solid form detectable marker in a sealed container to a temperature of from 2250 °C to 3000 °C to form particles comprising a detectable marker encased in a plurality of layers of carbon and being capable of binding to fibrin" and (2) "precipitating the particles to form the detectable reagent" (line 25, pg. 4 to line 2, pg 5), and notes that "generally the graphite crucible is heated in the presence of a substantially pure inert gas atmosphere within the sealed container" (lines 18 – 19, pg. 5). Support is also provided in the description of methods of forming diagnostic particles beginning on line 17 of page 12 and ending on line 4 of page 14.

Amendments to the Claims

Amendment of claims 80 - 82 is requested to more particularly point out and distinctly claim the present invention. Amended claims 80-82 now recite the limitation "wherein said particles exhibit a specific affinity for said fibrin." Support for these amendments is provided by the teaching on page 10, lines 10 -12 that diagnostic particles of the present invention exhibit "specific affinity" for fibrin. Support is also provided on page 15, lines 5 -6 wherein the "specific binding capacity for fibrin" of the present diagnostic particles is described, and in the summary of experimental results provided on page 15, lines 18 – 19 wherein "measurement showed that most of the particles were specifically bound to fibrin." In addition, support for this amendment is provided by the experimental results illustrated in Figures 1, 3 - 11, which demonstrate that the diagnostic particles of the present invention exhibit specific binding capacity for fibrin. The requested amendments do not introduce any new matter.

Amendment of claims 81 & 82 is also requested to recite "wherein said diagnostic particles are made by heating a carbon crucible having deposited thereon a detectable marker to a temperature in the range of 2250° C to 3000° C,

thereby generating suspended particles, and precipitating said suspended particles to form said diagnostic particles." Support for the these amendments is provided in the description of exemplary methods "for forming a detectable reagent for use in labeling fibrin" beginning on line 25 of page 4 and ending on line 19 of page 5 which provides a description of the steps of (1) "heating a carbon crucible having deposited thereon a solid form detectable marker in a sealed container to a temperature of from 2250 °C to 3000 °C to form particles comprising a detectable marker encased in a plurality of layers of carbon and being capable of binding to fibrin" and (2) "precipitating the particles to form the detectable reagent." Support is also provided in the description of methods of forming diagnostic particles beginning on line 17 of page 12 and ending on line 4 of page 14. The requested amendments do not introduce any new matter.

Amendment of claims 33 – 35, 61, 64, and 71 is requested to change their dependency such that they now all depend from claim 82. Amendment of claims 33 – 35, 61, 64, and 71 also changes the recitation "particles" to recite "diagnostic particles" to provide improved antecedent basis given their amended dependence from claim 82. The requested amendments improve clarity do not introduce any new matter.

Amendment of claims 68 is requested to change its dependency such that it depends from claim 61. The requested amendment corrects antecedent basis, improves clarity and does not introduce any new matter.

Rejections under 35 U.S.C. § 112

Claims 31, 33-35, 61, 64, 68, 71, and 80-85 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In support of this rejection the Examiner asserts that the phrase

"wherein said particles bind *directly* to said fibrin" does not have antecedent basis in the specification, claims, and/or drawings as originally filed.

Applicants disagree with the Examiner characterization of the specification, claims, and/or drawings as originally filed. To expedite prosecution and without acquiescing to the rejections, however, the limitation "wherein said particles bind *directly* to said fibrin "has been removed entirely from all the rejected claims. Accordingly, reconsideration and withdrawal of all the present rejections under 35 U.S.C. § 112, first paragraph, is requested.

Rejections under 35 U.S.C. § 103

Claims 31, 33-34, 71 and 80 – 85 is rejected under Section 103(a) as allegedly unpatentable over International Patent Application No. WO93/15768 (Watson *et al.*) in view of U.S. Patent No. 5,217,705 (Reno *et al*). In support of this rejection, the Examiner characterizes Watson *et al.* as teaching "non-diamond carbon allotropes, such as fullerenes, graphite and amorphous carbons, are used as diagnostic agents," and Reno *et al.* as teaching "a method of diagnosing blood clots using fibrin-binding proteins." With respect to the combined teaching of these references, the Examiner concludes that:

> [i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize a radiolabeled graphitic mesh entity of Watson et al. attached to a protein of Reno et al. in a method for detecting fibrin in a patient because (1) Watson et al. teaches the administration of the carbon allotropes of the invention therein to humans and nonhuman animals for diagnostic purposes; (2) Watson et al. teaches that the diagnostic agents taught therein may be attached to biomolecules such as proteins and cell adhesion molecules; (3) Watson et al. teaches that the carbon allotrope diagnostic entity of the invention therein is used as a carrier for radiolabels; (4) Reno et al. teaches administration of the a diagnostic agent for the detection of fibrin; and (5) Reno et al. teaches the attachment of a fibrin-binding protein attached to a detectable substance such as a radiolabel."

Applicants respectfully traverse these rejections. Amendment of the rejected claims is requested, however, to more clearly specify the claimed invention and expedite prosecution. Accordingly, Applicants request reconsideration and withdrawal of the rejections in light of the following arguments.

The inventions of rejected claims 31, 33-34, 71 and 80 – 85 are directed to methods for detecting fibrin which utilize administration and detection of diagnostic carbonaceous particles capable of forming a colloid upon dispersal into an aqueous medium and capable of binding to fibrin. Applicants show that the diagnostic carbonaceous particles of the present invention exhibit specific affinity for fibrin in a variety of experimental conditions, including *in vivo* conditions, and believe that they are the first ones to identify this property and use it in the methods of the present invention. (See e.g., pg. 2, lines 17 – 20, pg. 10, lines10 -13 & Examples 3 – 27, pages 14 – 26). The specific affinity for fibrin of the diagnostic particles of the present invention is a significant feature of the present invention because this characteristic provides for accurate, sensitive and selective labeling of fibrin which serves the basis of important diagnostic procedures and therapies relating to the detection and treatment of disease.

Claims 31, 33-34, 71 and 80 – 85 are not rendered obvious in light of the cited references because their combined teaching does not enable preparation and use of a diagnostic particle comprising a detectable marker encased in at least two layers of carbon and exhibiting specific affinity for fibrin. In the pending rejections, the Examiner relies upon a diagnostic composition allegedly enabled by the combined teaching of Watson *et al.* and Reno *et al.* consisting of a graphite particle having biologically active surface bound fibrin binding proteins (FBPs) capable of selectively binding to fibrin. The cumulative teaching of these references is deficient, however and does not enable preparation and use of the diagnostic composition relied upon by the Examiner because it does not provide any teaching or even guidance as to how to conjugate fibrin binding proteins to

the exterior surface of a graphite particle in a manner retaining their biological activity to fibrin. First, graphite is "one of the most chemically inert materials" (See, Section 7.1, pg. 63 of The Handbook of Carbon, Graphite, Diamond, and Fullerenes cited in the Office Action of April 10, 2004) and, therefore, functionalization to include surface bound proteins, if even possible, is expected to require conjugation reactions under very specific experimental conditions, which may not be compatible with maintaining the activity of labile species such as fibrin binding proteins. Second, Reno *et al.* teaches that fibrin binding proteins must be conjugated to a radiolabled marker in a very special and specific configuration to retain their biological activity to fibrin (*See* e.g., col. 5, lines 49 – 53 of Reno *et al.*, "non-specific attachment of radiolabeled compounds to FBPs may result in a decrease in the ability of the protein to bind to fibrin, since a portion of the radioisotopes will be attached to the FB domain"). The disclosure of the combined references fails to teach, however, a conjugation method capable of providing the specific configuration necessary for maintaining the biological activity of surface bound FBPs to fibrin. Applicants submit, therefore, that neither Watson *et al.* nor Reno *et al.* provide adequate teaching to enable one of ordinary skill in the art to synthesize and use a diagnostic particle consisting of a graphite particle having biologically active surface bound fibrin binding proteins capable of selectively binding to fibrin. Reconsideration and withdrawal of the pending rejections is respectfully requested.

Moreover, with respect to claims 33-34, 71 and 82 – 83, as amended with this response, the combination of Watson *et al.* and Reno *et al.* does not disclose or even suggest the limitation "wherein said particles are made by heating a carbon crucible having deposited thereon a detectable marker to a temperature in the range of 2250° C to 3000° C in an inert gas and in a sealed container, thereby generating particles suspended in said inert gas, and precipitating said particles suspended in said inert gas to form said diagnostic particles" and with respect to claims 80 and 81, as amended with this response, the combination of

Watson *et al.* and Reno *et al.* does not disclose or even suggest the limitation "wherein said diagnostic particles are made by heating a carbon crucible having deposited thereon a detectable marker to a temperature in the range of 2250° C to 3000° C, thereby generating suspended particles, and precipitating said suspended particles to form said diagnostic particles." Rather, the cumulative teaching of these references provides no disclosure or even guidance related to any methods of preparing graphitic carbon particulate, let alone the methods expressly set forth in claims as amended with this response. Therefore, amended claims 33-34, 71 and 80 – 83 are not rendered obvious by the cited combination of Watson *et al.* and Reno *et al.* because these references do not disclose or suggest all the limitations in the rejected claims.

Claim 35 is rejected under Section 103(a) as allegedly unpatentable over International Patent Application No. WO93/15768 (Watson *et al.*) in view of U.S. Patent No. 5,217,705 (Reno *et al*) and further in view of U.S. Patent No. 3,952,321 (Doherty *et al.*). In support of this rejection, the Examiner characterizes Doherty *et al.* as teaching "water, Ringer's solution, glucose in water and isotonic sodium chloride as acceptable vehicles for in vivo administration of active agents" and asserts "[i]t would have been obvious to one of ordinary sill in the art at the time of the invention to substitute the glucose in water, taught by Doherty et al., for the vehicles taught by the combined references."

Claims 61 and 68 are rejected under Section 103(a) as allegedly unpatentable over International Patent Application No. WO93/15768 (Watson *et al.*) in view of U.S. Patent No. 5,217,705 (Reno *et al*) in further view of U.S. Patent No. 5,330768 (Park *et al.*) and J. Phys. Chem. (Penfold *et al.*). In support of this rejection, the Examiner characterizes Park *et al.* as teaching "films for drug delivery comprised of poly(lactic acid) and polyethyleneoxide and polypropylene oxide" and Penfold *et al.* as teaching "$C_{16}EO_6$ as a known, beneficial nonionic

polyethylene oxide surfactant." The Examiner concludes that "[i]t would have been obvious to one of ordinary sill in the art at the time of the invention to coat the particle rendered obvious by Watson et al. and Reno et al. with a $C_{16}EO_6$ because (1) Watson et al. teaches that surfactants may be used with the diagnostic agents of the invention taught therein; (2) Penfold et al. teaches that $C_{16}EO_6$ is a known polyethylene oxide surfactant; and Park et al. teaches that films of polyethylene oxides are known to be used for forming films on agents administered in vivo."

Claims 64 is rejected under Section 103(a) as allegedly unpatentable over Watson *et al.* and Reno et al. in view of the Handbook of Cosmetic Science and Technology. In support of this rejection, the Examiner characterizes the Handbook of Cosmetic Science and Technology as teaching "that a reduction in size of the dispersed phase particles increases the stability of the colloid" and asserts "[i]t would have been obvious to one of ordinary sill in the art at the time of the invention to teach the dispersion of the combined references as nanodispersions . . . because of the expectation of achieving a more stable formulation."

Applicants respectfully traverse the rejections of claims 35, 61, 64 and 68 under Section 103(a). Amendment of the rejected claims is requested, however, to more clearly specify the claimed invention and expedite prosecution. The arguments set forth above with respect to claims 33-34, 71 and 80 – 83 are reasserted in the context of the rejections of 35, 61, 64 and 68. First, the cited combinations of references fails to enable preparation and use of the diagnostic particle relied upon by the Examiner comprising a detectable marker encased in at least two layers of carbon and exhibiting specific affinity for fibrin. Second, the cumulative teaching of these references provides no disclosure or even guidance related to any methods of preparing graphitic carbon particulate, let alone the methods expressly set forth in claims 35, 61, 64 and 68 as amended with this

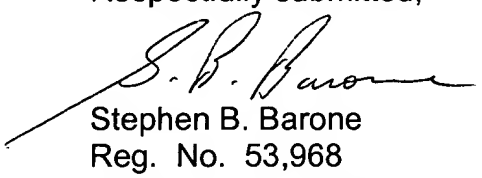
response. Accordingly, reconsideration and withdraw of the pending rejections of claims 35, 61, 64 and 68 is respectfully requested

CONCLUSION

In view of the foregoing arguments, this case is considered to be in condition for allowance and passage to issuance is respectfully requested. If new issues of patentability are raised, the Examiner is invited to call and arrange for an opportunity to discuss these issues via phone interview.

It is believed that a one month extension is required with this submission. Therefore, a petition for a one month extension and fee of $ 120.00 are provided. If this is incorrect, please deduct the appropriate fees for this submission along with any extension of time required from Deposit Account No. 07-1969.

Respectfully submitted,



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